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1. Your reference — SMC 60563/GB/P1

2. Patent application number *(The Patent Office will fill in this part)* — 0229243.1

16 DEC 2002
16DEC02 E771241-1 002944
P01/7700 0.00-0229243.1

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Avecia Limited
Hexagon House
Blackley
Manchester, M9 8ZS

Patents ADP number *(if you know it)*

07764137001

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

4. Title of the invention

Compounds and Process

5. Name of your agent *(if you have one)*

REVELL, Christopher

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Avecia Limited
Hexagon House
PO Box 42
Blackley
Manchester M9 8ZS

Patents ADP number *(if you know it)*

6969865001 7764137002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or

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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 16/12/02

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12. Name and daytime telephone number of person to contact in the United Kingdom

K.M.Pinder/G.Terry 0161 721 1361/2

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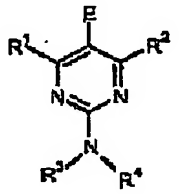
COMPOUNDS AND PROCESS

The present invention concerns a process for the preparation of pyrimidines and intermediate compounds useful in the preparation thereof.

According to a first aspect of the present invention, there is provided a process for the preparation of a compound of Formula (1):



Formula (1)

which comprises

a) reacting a compound of formula R^3-CO-CH_2-E with a compound of formula R^2-CHX^1X^2 in the presence of a compound of formula R^3R^4N-C(=NH)NH_2 and a catalyst, thereby to form a dihydropyrimidine; and

b) oxidising the dihydroprimidine produced in step a) to form the compound of Formula (1)

wherein

R^1 is an alkyl group;

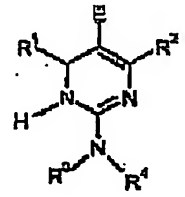
R^2 is an alkyl or aryl group;

R^3 and R^4 are each independently H, alkyl, aryl, a group of formula R^5SO_2-, wherein R^5 is alkyl or aryl, or R^3 and R^4 are linked to form, together with the nitrogen to which they are attached to form a 5 to 7 membered heterocyclic ring;

E is an electron withdrawing group; and

X^1 and X^2 are each independently leaving groups, or X^1 and X^2 together represent =O.

Dihydropyrimidines formed in step a) can be represented by the Formula (2):



Formula (2)

It will be recognised that the compounds of Formula (2) can exist in a number of tautomeric forms in which the double bonds are delocalised into other positions in the molecule, notably into different positions around the pyrimidine ring.

Alkyl groups which may be represented by R^1 include linear, branched and cyclic alkyl groups commonly comprising from 1 to 8 carbon atoms. Preferred cyclic alkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. Preferred linear and branched alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl and tert-butyl groups. Most preferably, R^1 represents isopropyl.

Alkyl groups which may be represented by R^2 are as described above for R^1.

Aryl groups which may be represented by R^2 include both homoaryl and heteroaryl groups, and commonly comprise at least one 6 to 7 membered aromatic ring. Examples of aryl groups include phenyl, naphthyl and pyridyl groups. Most preferably, R^2 represents a phenyl group.

Alkyl and aryl groups which may be represented by R^3, R^4 and R^5 are as described above for R^1 and R^2. When one of R^3 or R^4 represents a group of formula R^5SO_2-, it is preferably a mesyl or tosyl group. In certain preferred embodiments, R^3 represents methyl and R^4 represents mesyl. In other preferred embodiments, either or both of R^3 and R^4 are H.

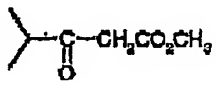
Alkyl and aryl groups which may be represented by R^1, R^2, R^3, R^4 and R^5 may be unsubstituted or substituted by one or more substituents. Examples of substituents include optionally substituted alkoxy (preferably C_{1-4}-alkoxy), optionally substituted alkyl (preferably C_{1-4}-alkyl), optionally substituted aryl (preferably phenyl), optionally substituted aryloxy (preferably phenoxy), optionally substituted heterocyclyl, polyalkylene oxide (preferably polyethylene oxide or polypropylene oxide), carboxy, phosphato, sulpho, nitro, cyano, halo, especially chloro and fluoro, ureido, $-SO_2F$, hydroxy, ester, $-NR^aR^b$, $-COR^a$, $-CONR^aR^b$, $-NHCOR^a$, carboxyester, sulphone, and $-SO_2NR^aR^b$ wherein R^a and R^b are each independently H, optionally substituted alkyl (especially C_{1-4}-alkyl) or optionally substituted aryl (preferably phenyl), or, in the case of $-NR^aR^b$, $-CONR^aR^b$ and $-SO_2NR^aR^b$, R^a and R^b together with the nitrogen atom to which they are attached may represent an aliphatic or aromatic ring system. Optional substituents for any of the substituents described may be selected from the same list of substituents.

Electron withdrawing groups which may be represented by E include nitro groups, nitrile groups, perhaloalkyl groups, such as trifluoromethyl and pentafluoroethyl, ester groups, especially alkyl carboxylate groups, sulphonamide groups, keto groups, amide groups, aldehyde groups, and groups of formula $-CH_2E^2$, wherein E^2 represents halo, especially bromo or chloro or a phosphorus-containing moiety, such as a phosphate ester, a phosphine or a phosphite ester. Preferably, E represents a group of formula $-CO_2(C_{1-4}$alkyl), and especially $-CO_2Me$.

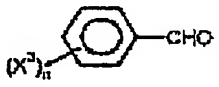
Leaving groups which can be represented by X^1 and X^2 include chloro, bromo and iodo, especially chloro, groups, and alkoxy groups, especially C_{1-4}alkoxy, such as methoxy, groups. Commonly, when X^1 and X^2 are leaving groups, either both are selected from chloro, bromo or iodo, or both are alkoxy. It is most preferred that X^1 and X^2 together represent =O.

Oxidising agents which may be employed in the process according to the present invention include those oxidising agents known in the art to oxidise dihydropyrimidines to pyrimidines. Examples of suitable oxidising agents include quinones, particularly substituted benzoquinones such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; transition metal oxidants such as ceric ammonium nitrate or sulfate, barium manganate, cadmium chloride and manganese dioxide; metallic oxidants, such as palladium on charcoal or other suitable platinum group metals; elemental sulfur; oxygen, especially atmospheric oxygen; and nitrosylsulfuric acid.

Preferred compounds of formula R^1-CO-CH_2-E are compounds of formula (C_{1-4}alkyl)-CO-$CH_2CO_2R^6$, wherein R^6 represents a C_{1-4} alkyl group, especially a methyl group. Most preferred compounds of formula R^1-CO-CH_2-E are compounds of formula:



Preferred compounds of formula R^2-CHX^1X^2 are compounds of formula:



wherein X^3 represents halo, and n is 0 or 1-5. Preferably X^3 is chloro or fluoro, alkyl, preferably methyl, or alkoxy, preferably methoxy. Most preferably n is 1, and X^3 is present at the 4-position. Especially preferred is 4-fluorobenzaldehyde.

Preferred compounds of formula R^3R^4N-C(=NH)NH_2 are guanidine, methylguanidine and N-methyl-N-mesylguanidine. The compounds of formula R^3R^4N-C(=NH)NH_2 can be employed as the free base, but in many embodiments are advantageously employed as a salt, especially a hydrochloride salt.

Catalysts which can be employed in the present invention include bases and acids.

Bases which can be employed in the process of the present invention are preferably inorganic bases. Examples of inorganic base include alkali and alkaline earth metal carbonates and hydrogencarbonates, particularly sodium or potassium carbonate and most preferably sodium or potassium hydrogencarbonate.

Acids which can be employed in the process of the present invention include both protic and Lewis acids. Examples of protic acids include mineral acids, such as hydrochloric, nitric and sulphuric acids and polyphosphate ester, or organic acids such as p-toluenesulfinic acid. Examples of suitable Lewis acids include $FeCl_3$, $NiCl_2$, boron trifluoride etherate and $InCl_3$. When a Lewis acid is employed, a protic acid such as HCl, may also advantageously be present.

Step a) of the process according to the present invention preferably employs a solvent which is inert under the reaction conditions employed. In may embodiments, a polar solvent is employed, preferably a polar aprotic solvent, for example including dichloromethane, dimethylsulphoxide and tetrahydrofuran. Preferred solvents are amides, such as N-methylpyrrolidinone and especially dimethylformamide.

Step b) of the process preferably employs a solvent which is inert under the reaction conditions employed. The solvent is selected according to the nature of the oxidising agent employed, and may include the solvents described above for step a). Further solvents which may be employed in step b) include non-polar solvents, for example hydrocarbons, such as toluene.

Compounds of Formula (2) and tautomers thereof are novel, and accordingly form a second aspect of the present invention.

Step a) of the process according to the first aspect of present invention forms a third aspect of the present invention.

Step b) of the process according to the first aspect of present invention forms a fourth aspect of the present invention.

When it is desired to produce a compound of formula (1) wherein one or both of R^3 and R^4 is not H, it will be recognised that the alkyl, aryl or SO_2R^5 moieties, particularly methyl and mesyl moieties, may be present in the compound of formula R^3R^4N-$C(=NH)NH_2$, may be introduced into a compound of formula (2) prepared where R^3 and R^4 are both H, prior to the oxidation in step b), or may be introduced into a compound of formula (2) prepared where R^3 and R^4 are both H.

The present invention is illustrated further, without limitation, by the following example.

Example

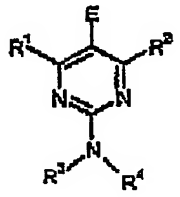
a) A 100 ml two neck round bottom flask equipped with a condenser and connected to a nitrogen line was charged with p-fluorobenzaldehyde (0.57ml, 5mmol), MIBA (0.79g, 6.5mmol), guanidine hydrochloride (1.19g, 12.5mmol), potassium carbonate (2.76g, 40mmol) and 10 ml of anhydrous dimethylformamide. This mixture was stirred and heated at 70°C for 20h. The reaction mixture changed from colourless to yellow during this time. After cooling, dimethylformamide was removed under vacuum and the residue

partitioned between brine (50ml) and ethyl acetate (200ml). The aqueous phase was washed with ethyl acetate (200ml) and the combined organic layers were dried over magnesium sulfate and filtered. The solvent was removed under vacuum to obtain 1g of yellow solid. ^{1}HNMR and LC showed methyl 2-amino-6-(4-fluorophenyl)-4-isopropyl-3,4-dihydropyrimidine-5-carboxylate as the major component (82%). This sample was characterised by comparison with a previously prepared standard.

b) A 25 ml three neck round bottom flask evacuated and back-filled with nitrogen was charged with methyl 2-amino-6-(4-fluorophenyl)-4-isopropyl-1,4-dihydropyrimidine-5-carboxylate (100 mg) and 15 ml of anhydrous THF. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (135 mg, 0.45 mmol) was added under nitrogen. The red solution was stirred at room temperature. After 40 min, methyl 2-amino-6-(4-fluorophenyl)-4-isopropylpyrimidine-5-carboxylate was observed by HPLC and LC-MS. The product was identified by comparison with a standard of high purity prepared by a different chemical route. Both samples co-eluted by HPLC and showed the same ions by positive and negative electrospray mass spectrometry.

CLAIMS

1. A process for the preparation of a compound of Formula (1):



Formula (1)

which comprises

a) reacting a compound of formula R^1-CO-CH_2-E with a compound of formula R^2-CHX^1X^2 in the presence of a compound of formula R^3R^4N-C(=NH)NH_2 and a catalyst, thereby to form a dihydropyrimidine; and

b) oxidising the dihydroprimidine produced in step a) to form the compound of Formula (1)

wherein

R^1 is an alkyl group;

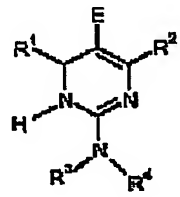
R^2 is an alkyl or aryl group;

R^3 and R^4 are each independently H, alkyl, aryl, a group of formula R^5SO_2-, wherein R^5 is alkyl or aryl; or R^3 and R^4 are linked to form, together with the nitrogen to which they are attached to form a 5 to 7 membered heterocyclic ring;

E is an electron withdrawing group; and

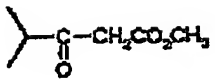
X^1 and X^2 are each independently leaving groups, or X^1 and X^2 together represent =O.

2. A process according to claim 1, wherein the dihydroprimidine is represented by the Formula (2), and tautomers thereof:

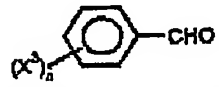


Formula (2)

3. A process according to claim 1 or claim 2, wherein the compound of formula R^1-CO-CH_2-E is a compound of formula:



4. A process according to any preceding claim, wherein the compound of formula R^2-CHX^1X^2 is a compound of formula:



wherein X^3 represents halo, and n is 0 or 1-5, and preferably 4-fluorobenzaldehyde.

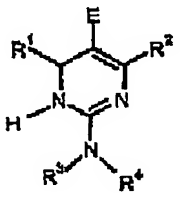
5. A process according to any preceding claim, wherein the compound of formula R^3R^4N-$C(=NH)NH_2$ is guanidine, methylguanidine or N-methyl-N-mesylguanidine.

6. A process according to claim 5, wherein the compound of formula R^3R^4N-$C(=NH)NH_2$ is employed as a hydrochloride salt.

7. A process according to any preceding claim, wherein the catalyst is a base, preferably an alkali or alkaline earth metal carbonate and hydrogencarbonate.

8. A process according to any preceding claim, wherein the oxidising agent is a quinone.

9. A compound of Formula (2), and tautomers thereof:



Formula (2)

wherein

R^1 is an alkyl group;

R^2 is an alkyl or aryl group;

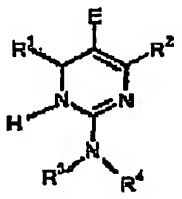
R^3 and R^4 are each independently H, alkyl, aryl, a group of formula R^5SO_2-, wherein R^5 is alkyl or aryl, or R^3 and R^4 are linked to form, together with the nitrogen to which they are attached to form a 5 to 7 membered heterocyclic ring; and

E is an electron withdrawing group.

10. A compound according to claim 9, wherein R^1 represents isopropyl, R^2 represents 4-fluorophenyl, and R^3 and R^4 each independently represents H, methyl or mesyl.

11. A compound according to claim 10, wherein R^3 is methyl and R^4 is mesyl.

12. A process for the preparation of a compound of Formula (2):



Formula (2)

which comprises

a) reacting a compound of formula R^1-CO-CH_2-E with a compound of formula R^2-CHX^1X^2 in the presence of a compound of formula R^3R^4N-C(=NH)NH_2 and a catalyst, thereby to form the compound of Formula (2)

wherein

R^1 is an alkyl group;

R^2 is an alkyl or aryl group;

R^3 and R^4 are each independently H, alkyl, aryl, a group of formula R^5SO_2-, wherein R^5 is alkyl or aryl, or R^3 and R^4 are linked to form, together with the nitrogen to which they are attached to form a 5 to 7 membered heterocyclic ring;

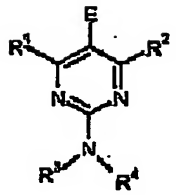
E is an electron withdrawing group; and

X^1 and X^2 are each independently leaving groups, or X^1 and X^2 together represent =O.

13. A process according to claim 12, wherein R^1 represents isopropyl, R^2 represents 4-fluorophenyl, and R^3 and R^4 each independently represents H, methyl or mesyl.

14. A process according to claim 13, wherein R^3 is methyl and R^4 is mesyl.

15. A process for the preparation of a compound of Formula (1):



Formula (1)

which comprises oxidising a compound of Formula (2) as claimed in claim 9, wherein

R^1 is an alkyl group;

R^2 is an alkyl or aryl group;

R^3 and R^4 are each independently H, alkyl, aryl, a group of formula R^5SO_2-, wherein R^5 is alkyl or aryl, or R^3 and R^4 are linked to form, together with the nitrogen to which they are attached to form a 5 to 7 membered heterocyclic ring; and

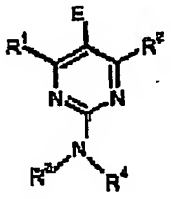
E is an electron withdrawing group.

16. A process according to claim 15, wherein R^1 represents isopropyl, R^2 represents 4-fluorophenyl, and R^3 and R^4 each independently represents H, methyl or mesyl.

17. A process according to claim 15 or 16, wherein the oxidation employs a quinone.

ABSTRACT
COMPOUNDS AND PROCESS

A process for the preparation of a compound of Formula



and intermediates useful therein are provided. The process comprises reacting a compound of formula R^1-CO-CH_2-E with a compound of formula R^2-CHX^1X^2 in the presence of a compound of formula R^3R^4N-C(=NH)NH_2 and a catalyst, thereby to form a dihydropyrimidine; and oxidising the dihydropyrimidine to form the compound of Formula (1). R^1 is an alkyl group; R^2 is an alkyl or aryl group; R^3 and R^4 are each independently H, alkyl, aryl, a group of formula R^5SO_2-, wherein R^5 is alkyl or aryl, or R^3 and R^4 are linked to form, together with the nitrogen to which they are attached to form a 5 to 7 membered heterocyclic ring; E is an electron withdrawing group; and X^1 and X^2 are each independently leaving groups, or X^1 and X^2 together represent =O.